

warfarin, somewhat arbitrarily in terms of prothrombin time (PT) ratios using United States thromboplastins as follows: ultra-low dose: PT ratio of 1.2 and below; low dose: PT ratio of 1.3 to 1.7; medium dose: PT ratio of 1.6 to 1.9; and high dose: PT ratio of 1.8 to 2.1. The use of ultra-low-dose warfarin—with or without low-dose aspirin—cannot be justified as the long-term clinical efficacy has not yet been established. Contrariwise, high-dose regimens cannot be accepted as the long-term risks of hemorrhage are excessive. The options, in this view, are reduced to the choice between low- and medium-dose prophylaxis that overlaps slightly.

There is no longer any question that recurrent venous thromboembolism can be prevented at the low-dose range. Whether arterial thromboembolism would be equally well contained by that regimen among group I patients, while reasonable from the pathologic viewpoint, has not yet been confirmed by adequate clinical trial. One further clinical observation, stated originally in 1950,¹ needs reemphasis: namely, that greater intensities of anticoagulant therapy are required immediately after the onset of an acute thrombotic process than are necessary to prevent recurrences.²

Support for some of the views expressed here comes from clinical trials reported since the manuscript by Stults and co-workers was accepted for publication.²⁻⁴ Moreover, after considering the variables inherent in the prothrombin time assay itself, in the many features that may promote bleeding, in the knowledge that administration may involve a lifetime of use, and that many of the patients most needing long-term prophylaxis are in their 70s and 80s, it would appear reasonable to suggest that a majority of the group I patients at risk of systemic embolism can probably be managed at the low-dose ratios. In deciding on low- or medium-dose warfarin regimens, one must appreciate that the terms "low-risk" and "high-risk" patients depend both on the accumulated risk factors that a patient brings to the present illness and on the degree of thrombogenicity induced by the illness itself. For patients in whom the combined risk factors add up to a low or medium risk, a low-dose regimen may be adequate. For high-risk patients, the medium-dose range may be necessary. The latter can be justified so long as both physician and patient appreciate that a greater risk of bleeding is incurred.

Group II patients present a greater challenge in the selection of PT ratios. It would be consistent with the view already expressed that group II patients should be considered for medium-dose prophylaxis with all the caveats that such a choice implies. If the latter fails—as will inevitably occur with any antithrombotic agent—a modality other than warfarin should be considered rather than commit a patient, long term, to the hemorrhagic risks of a high-dose regimen. This is particularly true among patients with cardiac and cerebrovascular disease in whom life-threatening thromboembolic events are uncommon or in whom the anticipated benefit of anticoagulation is modest.

Considering the state of the art, the indications for prophylaxis detailed earlier should be construed as suggestions rather than mandates, since they do not all represent a broad consensus and will undoubtedly undergo modifications with time. The difficulty in advising physicians as to which conditions and at what intensity anticoagulation should be employed today is best epitomized by the English novelist Samuel Butler's 1912 view: "Life is the art of drawing sufficient conclusions from insufficient premises."⁵(p11)

In regard to the prothrombin time itself, there are practical

recommendations concerning the performance of the assay per se as well as the manner in which the results are reported that can influence favorably the precision with which warfarin is administered. Organizations responsible for the approval of clinical laboratories should require that blood specimens for prothrombin times be collected in what are classified as "clinical grade," polymer-lined tubes such as polypropylene and *not* in glass or imperfectly siliconized glass vessels. The availability of a "clean" polymer vacuum tube containing sodium citrate would facilitate the practicality of this recommendation. The artifactual shortening of the prothrombin time when blood is collected in glass or imperfectly siliconized glass tubes begins within an hour, is pronounced within two to four hours after venipuncture, and can readily lead to drug overdose.⁶ Clinical laboratories are also remiss if they do not at least report their control values with each patient's prothrombin time. In addition, the ratio of a patient's prothrombin time to the control value should be provided, for that is the actual piece of information on which dosage is based. Clinical laboratory resistance to these recommendations must reckon with the reality that, for the foreseeable future, a prothrombin time will remain the effective means of regulating the dose of warfarin—the drug of choice for thousands of patients at risk of pulmonary and systemic thromboemboli.

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Alcohol and the Cardiovascular System

IN THIS ISSUE OF THE JOURNAL, Davidson has extensively reviewed the multiple effects that ethyl alcohol may have on the cardiovascular system, which may be either harmful or potentially beneficial. Among the harmful effects is the capacity of ethanol to induce heart failure when chronically abused. As a separate phenomenon, the effects on cardiac conduction and rhythm are analyzed. Of particular note is the increased risk of sudden death in heavy drinkers. The epidemiologic evidence linking alcohol to hypertension and stroke and its putative preventive role in coronary artery disease are examined. It is noteworthy that the variability of the target organ affected by chronic alcoholism implies a difference in genetic susceptibility of cells that renders individual tissue prone to ethanol toxicity.

Davidson elaborates several weaknesses in the linkage of modest ethanol use to a reduction of coronary artery disease manifestations. Factors other than the moderate use of ethanol may be implicated. Patients in this subset tend to have lower basal arterial pressure and body weight.¹ Further-

more, they appear to have a lower intake of total saturated fat and a higher intake of polyunsaturated fatty acids.² A persistent flaw has been the composition of the control group. It is believed that there are sufficient ex-drinkers in this group to compromise its validity, since they share a number of characteristics that increase their cardiovascular risk. These include a higher prevalence of cigarette smoking, obesity, and hypertension compared with those who were never drinkers.¹ Moreover, they are likely to be unmarried and to work in manual occupations. In the final analysis, if modest alcohol ingestion proves to have a preventive effect, its usefulness as a general public health measure would be limited by potential addictive consequences.

At the other end of the population spectrum, the effect of substantial use may be underestimated by the nonparticipation of heavy drinkers in large-scale studies. Their identification adds significantly to this field because they are at increased cardiac risk.³

In terms of heart failure and its prevalence in the alcohol-abusing population, this is difficult to determine because of the methodologic difficulties discussed by Davidson. When considered in relation to other forms of congestive cardiomyopathy, ethanol use has been found to be the etiologic factor at a range between 21% and 32% of cases.³ The assumption that the incidence may be higher at institutions that serve a population with a relatively high incidence of alcoholism appears reasonable.⁴

A variety of studies support the belief that there is a relatively long gestational period before the clinical appearance of cardiac disease, analogous to that of liver disease. Most studies examining addicted persons without clinical evidence of heart disease find an incidence of subclinical abnormalities approximating 50% by noninvasive testing.⁵ In middle-aged men who have been drinking heavily for ten years or more, an echocardiogram may reveal an increased thickness of the interventricular septum and posterior left ventricular wall without an abnormality of the ejection fraction or chamber diameters. That the earliest abnormalities are related to diminished compliance has been supported by the finding of a notable increase of the end-diastolic pressure with a slight reduction of the end-diastolic volume.⁵ Moreover, contractile velocity indices are diminished at this stage when the ejection fraction may not be substantially abnormal. There is suggestive evidence that when a patient becomes abstinent at this stage of the disease, the process may be reversed. Certainty on this point, however, requires larger scale, long-term studies.

Cardiac decompensation typically occurs in men between 30 and 55 years of age who have ingested at least 80 grams of alcohol on most days for at least ten years. When left ventricular dysfunction progresses to low-output heart failure, exertional or nocturnal dyspnea occurs. Weakness and fatigue may be prominent complaints. Physical signs of cardiac decompensation are similar to those observed with other forms of congestive cardiomyopathy.

Cardiomegaly may be due to the primary myocardial process or to mitral regurgitation related to papillary muscle insufficiency. An associated apical murmur is characteristically confined to a portion of systole and as a rule changes as cardiac compensation is restored. Because an addicted person may frequently delay seeking medical assistance for weeks to months, evidence of right-sided heart failure is not uncommon, with distended jugular veins, an enlarged tender

liver, and edema of the dependent portions of the body. This may be erroneously identified as primary right-sided heart failure.

It is noteworthy that even before this stage, the presence of poor R wave progression on a precordial electrocardiogram may suggest coronary artery disease. Coronary angiography, however, usually reveals normal vessels.

A variety of atrial dysrhythmias have been described in patients without overt cardiomyopathy or enlarged hearts. Acute intoxication is typically superimposed on a background of alcoholism. Characteristically atrial fibrillation is the most common arrhythmia, and plasma electrolytes are usually normal. Sinus rhythm may be restored spontaneously in some but usually requires cardioversion or pharmacologic intervention. After a normal sinus rhythm was restored, moderate conduction delays were found on a high-speed electrocardiogram and were considered to be the background for the induction of acute arrhythmias.⁶

Moreover, in an analysis of new-onset atrial fibrillation in 40 patients younger than 65 years, alcohol use was considered to be causative or contributory in approximately two thirds.⁷ This phenomenon has been reproduced in electrophysiology laboratories.

In view of these observations, it is surprising that evidence of ventricular tachycardia in these patients is sparse. One explanation could be that ventricular tachycardia in alcoholic patients rapidly progresses to fibrillation before medical assistance. Although several reports from medical examiners in this country have indicated a high incidence of sudden death in persons who abuse ethanol, this issue has been more fully delineated in a prospective study of sudden death at the Pathology Institute in Moscow. The authors revealed that 17% of these deaths were related to alcohol abuse, and these were predominantly in patients younger than 50.⁸ None could be attributable to sleep apnea; inclusion in the study required that the event be witnessed and that death occur within 30 minutes of symptoms. Significant coronary artery disease was absent in these patients, but evidence of cardiomyopathy by light and electron microscopy was present in specimens taken within hours of death.

Although social drinking is often associated with a small rise of the systolic arterial pressure, persons who habitually imbibe heavily often show rises of systolic and diastolic pressure that may be substantial. These hypertensive responses are not related to a high-output state, since peripheral arterial resistance is substantially increased.⁹ Transient pressure elevations in nonalcoholic persons are not considered to give rise to myocardial disease, and in an addicted person this transient hypertensive state is commonly unassociated with clinically significant heart disease. As indicated, it is hoped that this issue will soon be clarified.

Whether fixed hypertension can develop in persons who have frequent vasoconstrictive responses to ethanol withdrawal is not clear. Studies of cardiac function in alcoholic patients, when carried out days to weeks after the last ethanol consumption, have shown normal arterial pressure in the preclinical state, mild heart failure, or failure after compensation.³ Moreover, in none of these studies were such consequences of hypertension as retinopathy reported.

Epidemiologic studies have indicated a positive association between the amount of alcohol consumed and the development of cerebrovascular accidents. This relationship is most notable in patients younger than 50 years and includes

hemorrhagic and nonhemorrhagic events.¹⁰ The former were even found in middle-aged women who consumed moderate amounts.

Although this phenomenon has been reported to be independent of blood pressure readings, a transient pressure elevation before and during a stroke has not been excluded. More important, patients who reduce their alcohol intake apparently have a considerably lower risk of hemorrhagic stroke developing than those who maintain their usual intake, but additional prospective studies are required to confirm this observation.

In all of the syndromes mentioned earlier, an accurate history of alcohol abuse may not be readily obtained. Alterations in the composition of blood may aid in the diagnosis. The mean corpuscular volume of the red cell may be increased as well as liver enzyme concentrations. The γ -glutamyl transferase measurement appears particularly useful. Albumin and urea levels may be reduced and high-density lipoprotein and transferrin concentrations enhanced. While not available currently in routine clinical laboratories, an analysis of platelet membranes may be particularly useful. Membrane activity of monoamine oxidase and adenylate cyclase, while normal in the basal state, shows reduced responses to biochemical stimulations that appear to persist for months to years after abstinence is begun.¹¹

Although endomyocardial biopsy has not been particularly useful, skeletal muscle is a readily available tissue for biopsy in identifying alcoholism. Atrophy of striated muscle fibers has been reported particularly of type IIB fibers, which is a relatively specific finding.¹²

The salient feature of long-term management for all of the cardiovascular consequences of alcoholism is abstinence, which has been associated with a decline in the incidence of stroke and hypertension. On the basis of a four-year follow-up study of patients presenting with cardiac decompensation, this also appears to apply to the myocardial complications. A third were found to have apparently maintained abstinence, and the majority of these had an improved or unchanged cardiac status, with a 9% mortality.¹³ Because

20% of those who were allegedly abstinent deteriorated in cardiac status, at certain stages of the disease the pathogenic mechanisms may continue unabated. More than half of those who remained actively alcoholic died.

Heart failure is traditionally managed medically, and treatment is guided by the severity of the process. In view of the high incidence of mural thrombi, anticoagulation can be used if the coagulation system is relatively normal and the patient is currently abstinent. When a patient is actively alcoholic, this therapy should not be applied. It should be noted that in this circumstance, therapy for those with chronic essential hypertension is also relatively ineffective.

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